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(54) Title: NOVEL COMPOSITIONS OF CARVEDILOL

(57) Abstract: This invention relates to a novel composition of comprising carvedilol, and methods of using the composition to treat hypertension, congestive heart failure and angina.

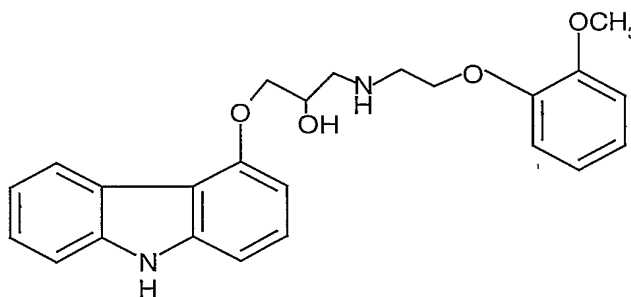
NOVEL COMPOSITIONS OF CARVEDILOL

Field of the Invention

This invention relates to novel compositions of carvedilol and to the use of such
5 compositions in the treatment of hypertension, congestive heart failure and angina.

Background of the Invention

The compound, 1-(carbazol-4-yloxy-3-[[2-(o-methoxyphenoxy)ethyl]amino]-2-
propanol, is known by the name "carvedilol" and is the subject of U.S. Patent No. 4,503,067
10 (the 067 patent), issued March 5, 1985. This compound has the following structure:



Carvedilol is useful in the treatment of hypertension, congestive heart failure and angina.

The oral absorption of carvedilol is significantly reduced as it travels through the GI tract because of its poor solubility near neutral pH. The goal of the instant invention is two-
15 fold: 1) the release of carvedilol must be controlled from the dosage form, and 2) the absorption of carvedilol must be enhanced in the lower part of the GI tract. In order to increase the absorption of Carvedilol in the lower part of GI tract, the formulation strategy was to combine the nanoparticle formulation with a solubilizer/release modifier approach in the dosage form. The rationale for the nanoparticle formulation was to enhance the
20 dissolution of carvedilol once it was released from the dosage form.

It is known that pharmaceutically active compounds may be subjected to milling procedures to obtain a particle size appropriate for tablet formation and for other formulation types. Air jet milling and fluid energy milling (micronising) have been favored because of the reduced risk from introducing contamination from mill materials. However,
25 wet milling processes have been proposed for preparation of finely divided particles for pharmaceutical use, for example see U.S. Patent No. 5,145,684. This patent discloses a wet milling procedure to produce particles of a crystalline drug substance having a surface modifier adsorbed on the surface thereof in an amount sufficient to maintain an effective average particle size of less than about 400 nm. This particulate composition as a stable
30 suspension is said to provide improved bioavailability for poorly water soluble compounds.

According to the instant invention, it has been found that carvedilol can be formulated in novel compositions. These novel compositions have enhanced bioavailability.

Summary of the Invention

5 The present invention provides novel compositions comprising carvedilol.

This invention also provides for the use of such compositions for the treatment of hypertension, congestive heart failure and angina.

Description of the Invention

10 According to the present invention, compositions of carvedilol are provided wherein carvedilol is present in a spray-dried powder. The compositions are prepared using a process that involves wet bead milling and spray-drying. Compositions are prepared by admixture and, thus, they are suitably adapted for oral, parenteral or pulmonary administration. The compositions may be formulated in the form of tablets, capsules,
15 reconstitutable powders or suppositories. Orally administrable formulations are preferred.

The compositions of this invention are most suitably prepared by wet bead milling carvedilol in a one-chamber mill or a multi-chamber mill, for example a three-chamber mill, using grinding beads, such as YTZ grinding beads, having a particle size of from about 0.3-1.0 mm. Carvedilol suspensions are prepared by initially combining and mixing water
20 and excipients until the excipients are dissolved, followed by the addition of carvedilol. A number of additives could be used to make a more stable carvedilol nanosuspension, such as Pluronic F68 and Pluronic F127, particularly Pluronic F127. The resulting carvedilol suspensions are homogenized prior to wet milling using an air mixer. The chamber mill is then filled with the grinding beads and the agitator is set to run at a speed of from about
25 1500-2500 rpm. In the next step of the process, the carvedilol suspensions are circulated through the mill and the milling process is stopped after the average particle size is from about 700-500 nm. Prior to spray-drying, excipients are added into the milled carvedilol suspension and the resulting suspension is homogenized. Spray-drying, for example using Niro Mobile Minor Spray Dryer, is then carried out.

30 According to the instant invention, the carvedilol suspensions hereinbefore described are comprised of 30.0% of carvedilol and 6.0% of Pluronic F127. Additionally, the preferred excipients added to the milled carvedilol suspension are polyvinylpyrrolidone (PVP) and cellulosic polymers, for example hydroxyethylcellulose (HEC). The preferred composition of the spray-dried powder is: 10 parts of carvedilol, 2 parts of Pluronic F127, 1
35 part of PVP K30, and 2 parts of HEC. The preferred spray-drying conditions are low inlet

temperature (100 °C) and low outlet temperature (45 °C) for producing carvedilol spray-dried powder with an average particle size of 700-800 nm when it was reconstituted in water.

5 Tablets and capsules for oral administration are usually presented in a unit dose, and contain conventional excipients such as binding agents, fillers and diluents (tableting or compression aids), lubricants, disintegrants, colorants, flavorings, and wetting agents. The tablets may be coated according to techniques well known in the art.

10 These solid compositions may be prepared by conventional methods of blending, filling, tableting, or the like. Repeated blending operations may be used to distribute the active agent throughout those compositions employing large quantities of fillers. Such operations are, of course, well known in the art.

15 Oral formulations also include conventional controlled release formulations, such as tablets or pellets, beads or granules, having a sustained release or an enteric coating, or otherwise modified to control the release of the active compound, for example by the inclusion of gel forming polymers or matrix forming waxes.

20 Thus, the present invention provides a novel composition which comprises carvedilol. The composition is adapted for oral administration. The composition is presented as a formulation in a unit dose. Such a formulation is taken once or twice daily, preferably once daily. The preferred unit dosage form includes tablets or capsules.

 No unacceptable toxicological effects are expected when carvedilol is administered in accordance with the present invention.

 The following examples are illustrative of the instant invention. These examples are not intended to limit the scope of this invention as defined hereinabove and as claimed hereinbelow.

EXAMPLES

Example 1 – Bead Milling

Table 1. Formulations and particle size results of carvedilol wet bead milled suspensions

Batch	Suspension Composition			Milling Time (min.)	D10 (um)	D50 (um)	D90 (um)	D99 (um)
	Composition	% Composition	Composition ratio					
#1	Carvedilol Pluronic F68 Water	24.8% 7.4% 67.8%	10 3	300	0.26	0.68	1.37	2.57
#2	Carvedilol Pluronic F127	30.0% 3.0% 67.0%	10 1	150	0.21	0.58	1.19	2.74
#3	Carvedilol Natrosol (HEC)	30.0% 2.1% 67.9%	10 0.69	150	0.34	0.89	21.48	34.56
#4	Carvedilol Pluronic F127	23.7% 3.6% 72.7%	10 1.5	300	0.17	0.51	1.10	1.76
#5	Carvedilol Pluronic F127 Natrosol 250L (HEC) Water	20.5% 4.1% 2.0% 73.2%	10 2 1	240	0.20	0.57	1.16	1.87
#6	Carvedilol Pluronic F127 Natrosol 250L (HEC) Water	30.0% 6.0% 0.3% 63.7%	10 2 0.1	180	0.20	0.59	1.27	3.20
#7	Carvedilol Pluronic F127 Natrosol 250L (HEC) Water	30.0% 9.0% 0.3% 60.7%	10 3 0.1	240	0.19	0.56	1.16	1.91

#8	Carvedilol Pluronic F127 PVP K-30 Water	29.9% 6.0% 0.6% 63.5%	10 2 0.2	180	0.20	0.58	1.17	1.87
#9	Carvedilol Pluronic F127	30.05% 6.0% 64.0%	10 2	210	0.19	0.56	1.18	2.05
#10	Carvedilol Klucel (HPC)	22.5% 4.5% 73.0%	10 2	150	0.25	0.84	2.37	8.47

Ten batches of carvedilol suspensions with a variety of formulas (cf. Table 1) were milled using a one-chamber mill LMZ2. The required amounts of water and excipients were combined and mixed until the excipients dissolved. Carvedilol (3.6 kg per batch) was then added, and the resulting carvedilol suspensions were homogenized prior to wet milling using an air mixer.

The chamber was filled at 87-88% of capacity with 0.3 mm YTZ grinding beads. The agitator was running at a speed of 2000 to 2500 rpm. The carvedilol suspensions were circulated through the mill at a low flow rate (less than 2 L/min). Approximately 5 mL sample was collected every 30 minutes for in-process particle size analysis. The milling was stopped after the average particle size of carvedilol was reduced to 700 to 500 nm, with the total milling time ranging from 2.5 to 5 hours. The milled carvedilol suspensions were finally collected into white HDPE containers, and then stored at 5 °C.

Example 2 – Bead Milling

Three batches of carvedilol suspensions with the same formula (30.0% of Carvedilol and 6.0% of Pluronic F127) were prepared and pre-mixed using the same procedure described above. Each batch used 3.3 kg drug substance.

A three-chamber mill, DENA DS300, was used. Each chamber was filled with 1200 mL YTZ grinding beads: 1.0 mm beads for the first in-line chamber, 0.65 mm beads for the second in-line chamber, and 0.4 mm beads for the third in-line chamber. The agitators were run at a speed of 1500 rpm. Approximately 5 mL suspension was collected every 30 or 60 minutes for in-process particle size analysis. The milled carvedilol suspensions were finally collected in stainless steel containers and held at 5 °C until commencing the spray-drying process.

Example 3 – Spray Drying

The spray drying was carried out with a Niro Mobile Minor 2000 Spray Dryer (two fluid 0.8 mm nozzle, co-current spraying, Nitrogen gas). Prior to spray drying, necessary excipients were added into the milled Carvedilol suspension and the resulting suspension was homogenized for approximately 30 minutes. Later in development, a PVP/cellulose solution was prepared, held at 5 °C overnight and then mixed with the milled carvedilol suspension prior to spray drying. The carvedilol suspension was then spray-dried. The spray-dried powder was collected using glass bottles.

Example 4 – Spray Drying

A Niro Mobile Minor Spray Dryer was used. The carvedilol suspension was prepared using the procedure described above. The selected suspension formula contained 15.0% Carvedilol, 3.0% Pluronic F127, 1.5% PVP K-30, 3.0% HEC and 77.5% water.

The process parameters used for spray drying are listed in Table 2. Spray-dried powder was collected under Cyclone using glass containers. Samples were taken for particle size analysis.

Table 2. Parameters used for spray-drying process

Nozzle Pressure	Nozzle N ₂ Feed Rate	N ₂ Feed Rate to Chamber	Suspension Spray Rate	Inlet Temperature	Outlet Temperature
3 bar	5-5.5 bar	30 mmWG	~ 1.2 kg/h	100 °C	43-45 °C

Particle size distributions were measured by laser diffraction. All reported particle size data were obtained using the following: R1 lens, HRLD, Quixel, 600 rpm.

Example 5 – Alternate Preparation of Bead-Milled Intermediate

37 grams zirconium oxide grinding media (0.3 mm particle size)
3 grams water
0.15 grams Pluronic F127
1 gram carvedilol

The above components are combined in a beaker and the resulting slurry is agitated at 1500 rpm with an overhead mixer.

- 5 It is to be understood that the invention is not limited to the embodiments illustrated hereinabove and the right is reserved to the illustrated embodiments and all modifications coming within the scope of the following claims. The various references to journals, patents and other publications which are cited herein comprise the state of the art and are incorporated herein by reference as though fully set forth.

What is claimed is:

1. A pharmaceutical composition comprising carvedilol in spray-dried form.
- 5 2. A composition according to claim 1 wherein the carvedilol concentration is between 10% and 40%.
3. A composition according to claim 1 wherein the carvedilol concentration is about 30%.
- 10 4. A composition according to claim 1 wherein Pluronic F68 or Pluronic F127 is present.
5. A composition according to claim 1 wherein Pluronic F127 is present.
- 15 6. A composition according to claim 1 wherein the carvedilol concentration is about 30% and the concentration of Pluronic F127 is about 6%.
7. A composition according to claim 1 wherein the spray-dried powder is comprised of 10 parts carvedilol and 2 parts Pluronic F127.
- 20 8. A composition according to claim 1 wherein the spray-dried powder is comprised of 10 parts carvedilol, 2 parts Pluronic F127, 1 part polyvinylpyrrolidone K30 and 2 parts hydroxyethylcellulose.
- 25 9. A composition according to claim 1 prepared by wet bead milling and spray-drying.
10. A composition wherein the average particle size of carvedilol is about 30 700-500 nm.
11. A method of treating hypertension, congestive heart failure or angina which comprises administering to a subject in need thereof an effective amount of the composition according to claim 1.

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12. The use of the composition according to claim 1 in the manufacture of a medicament for the treatment of hypertension, congestive heart failure or angina.